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Skeletal Hyperostosis in Patients Receiving Chronic, Very-Low-Dose Isotretinoin

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• *Background and Design.*—We conducted a prospective roentgenographic survey of patients participating in a randomized, placebo-controlled, multicenter clinical trial that evaluated the effectiveness of chronic, very-low-dose (approximately 0.14 mg/kg per day for 3 years) isotretinoin in preventing the subsequent occurrences of new basal cell carcinoma in patients with previous basal cell carcinoma. To assess potential skeletal changes, a sample of 269 patients from among a total of 981 enrollees were randomly selected for comparative roentgenographic review. Baseline and 36-month roentgenograms of the cervical and thoracic spine of each patient were read side by side by a radiologist, masked to treatment group, who noted both the presence and extent of abnormalities at each vertebral level at baseline and the progression of existing or occurrence of new abnormalities at previously unaffected levels at 36 months.

Results.—In comparison with the placebo group, significantly more patients in the isotretinoin group exhibited progression of existing hyperostotic abnormalities (40% vs 18%; $P<.001$) and new hyperostotic involvement at previously unaffected vertebral levels (8% vs 1%; $P=.015$).

Conclusion.—Our findings indicate that chronic, very-low-dose isotretinoin can induce hyperostotic axial skeletal changes similar to those reported in patients taking higher doses.

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Ankylosing vertebral hyperostosis of the spine is a frequent roentgenographic finding characterized by ossification along the anterior margins of vertebral bodies and/or disk spaces. Typically, the hyperostotic ossification is located in the thoracic spine, but can also be found in the cervical and lumbar spine.[1-4] The disorder has been known for several decades under several synonyms. The term *diffuse idiopathic skeletal hyperostosis* was proposed by Resnick et al[5] based on observations of hyperostotic ossification at extraspinal sites. Although the cause of diffuse idiopathic skeletal hyperostosis is unknown, it may be linked to an abnormal metabolism of vitamin A.[6-9] It is more common in older populations,[10] males,[11] the obese, and type 2 diabetics.[12]

See also p 975.

Synthetic derivatives of vitamin A, including isotretinoin (13-*cis*-retinoic acid), have been in use since the middle of the 1970s to treat cystic acne, hereditary scaling disorders, and other dermatologic conditions. Pittsley and Yoder[13] first described an ossifying diathesis resembling diffuse idiopathic skeletal hyperostosis in patients taking high-dose isotretinoin (>2 mg/kg per day) for disorders of keratinization. Since then, several articles linking isotretinoin and other synthetic retinoids with hyperostotic changes in both the axial and appendicular skeleton have been published.[14-28] In the isotretinoin articles, patients studied were generally young (<40 years old) and received doses ranging from 0.5 to 3 mg/kg per day over periods of 4 months to 9 years. Although many of these studies were prospective in nature and some used age-matched control subjects, none had the advantage of being

conducted within the structure of a randomized, placebo-controlled clinical trial. We present the results of prospective roentgenographic survey of a random sample of patients participating in a trial that evaluated the effectiveness of chronic, very-low-dose isotretinoin (approximately 0.14 mg/kg per day for 3 years) in preventing the subsequent occurrences of new basal cell carcinomas (BCCs) in patients with prior BCC.

PATIENTS AND METHODS

Clinical Trial

A detailed description of the trial's design and the baseline characteristics of the participants has been published.[29] The study was a randomized, double-masked, placebo-controlled trial conducted by the National Cancer Institute, Bethesda, Md. Between 1984 and 1987, 981 participants were enrolled into the trial at eight clinical centers in the United States. To be eligible to participate, a patient had to be a white man or woman between the ages of 40 and 75 years; have had two or more biopsy-proven BCCs during the 5 years before randomization; have normal liver and renal functions; give written, informed consent; be willing and able to participate for the duration of the trial; have entire skin surface evaluable for presence of BCC; agree not to take high-dose vitamin A (>5 000 U/d); and, for women, be incapable of childbearing. After a screening visit to determine eligibility and obtain written informed consent, patients were randomized to take either 10 mg of isotretinoin (two 5-mg capsules once daily) or a matching placebo (both supplied by Hoffmann-LaRoche, Nutley, NJ) and enrolled into the trial. To monitor for skin cancer, potential treatment toxicity, and compliance, trial participants were scheduled for follow-up visits at 2 weeks, 3 months, 6 months, and every 6 months thereafter for the 3-year duration of the intervention.

All patient follow-up on the trial ended in June 1991. Analysis of data from the 3-year intervention period indicated that chronic, very-low-dose isotretinoin was not effective in preventing the occurrence of new BCC tumors in patients with previous BCC.[30]

Roentgenographic Survey

All randomized trial participants received cervical and thoracic lateral roentgenograms at the baseline and 36-month visits. To evaluate potential skeletal changes, a sample of 269 patients (139, isotretinoin group; 130, placebo group) was randomly selected from the entire patient population (n=981) using a computer-generated algorithm[31] for comparative review of their roentgenograms. The size of the sample was limited by the need to perform this roentgenographic review in a comprehensive and timely manner.

The roentgenograms were read by a board-certified radiologist (R.F.K.), with expertise in skeletal radiology and previous experience in examining x-ray films for retinoid-induced skeletal changes. The radiologist was masked to the treatment assignment and completed the review in two sessions. Baseline and 36-month roentgenograms for each patient were read side-by-side by the radiologist who noted both the presence and extent of baseline abnormalities (ie, hyperostoses, degenerative spondylosis, compression fractures, congenital abnormalities, and ankylosing spondylitis) at each vertebral level (C1 through T12) and the progression of existing abnormalities or the occurrence of new abnormalities at previously unaffected vertebral levels at 36 months. Only those findings that were considered by the radiologist to be extensive enough to be unequivocal were recorded as "definite" findings. Data were collected using a standardized data collection system on a personal computer.

Table 1.—Baseline Characteristics of the Random Sample of Patients Whose Roentgenograms Were Reviewed*

Characteristic	Isotretinoin, % (n=139)	Placebo, % (n=130)
Age, ≥64 y	45	50
Sex, M	80	78
Body mass index, >25.8	52	47
Diabetes mellitus, yes	5	5

*N=269.

Table 2.—Patients With Spinal Ligament Calcification and/or Vertebral Hyperostoses Detected by Roentgenogram After 36 Months of Treatment

Type of Change	Isotretinoin, No. (%) (n=139)	Placebo, No. (%) (n=130)	P*
Progression of existing ligament calcification or vertebral hyperostoses	56 (40)	24 (18)	<.001
New ligament calcification or vertebral hyperostoses†	11 (8)	2 (1)	.015

*Test for the difference between two proportions (χ^2 statistic).
†Of previously unaffected vertebral level.

To assess interobserver variability in roentgenographic interpretation, a second board-certified radiologist, also expert in skeletal radiology, read a sample of cases (28 patients from the cohort of 269) randomly selected from previously read roentgenograms using the same method and data collection system as the first reader. Intraobserver variability was evaluated by having the primary reader (R.F.K.) re-review the same random sample of roentgenograms while blinded to his first interpretations. Both interobserver and intraobserver variability in roentgenographic diagnoses were assessed by calculating the concordance between the second and first reading and are reported as percent agreement.

In the sample of 28 cases selected for re-review, there was little interobserver or intraobserver variation in the overall interpretation of the roentgenograms. Agreement on interpretation between the two radiologists reading the same films exceeded 96%, while intraobserver agreement for the sample was 92%.

Statistical Analyses

Treatment group comparisons were analyzed using the standard test for the difference between two proportions.[32] Reported *P* values are two sided. We used logistic regression analysis[31] to determine if other potential risk factors (eg, age, sex, body mass index [weight/height^2], diabetes mellitus) influenced our results or had an independent effect on the risk of developing skeletal changes.

RESULTS

Baseline characteristics of the random sample of patients selected for roentgenographic review are presented by the treatment group in Table 1. The median age of patients in this cohort was 63 years old. Men outnumbered women by almost four to one. There were no statistically significant differences for any of these characteristics between this sample and the overall

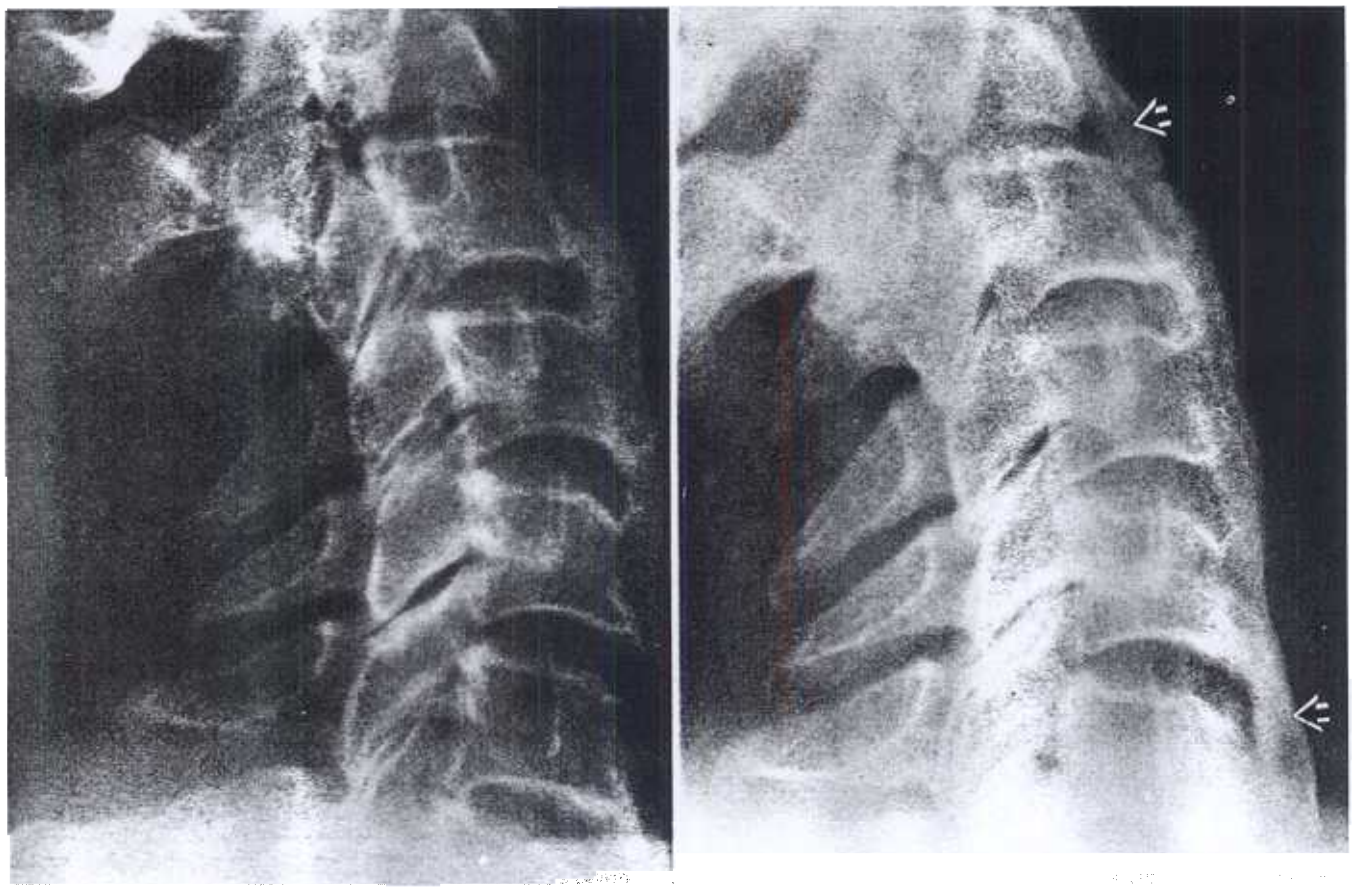

Fig 1.—Left, A 68-year-old man has vertically oriented thickening hyperostosis of the anterior spinal ligament in the cervical spine in this pretreatment roentgenogram. Right, After 36 months of isotretinoin therapy the ankylosis of the anterior spinal ligament has progressed to involve the C2-3 and C5-6 levels (arrows).

trial population (n=981) or the treatment and control groups within the sample.

The baseline cervical and thoracic roentgenograms of the 269 patients reviewed showed a variety of abnormalities associated with aging including ankylosing vertebral hyperostosis, degenerative spondylosis, ankylosing spondylitis, and compression fractures. At baseline, none of the patients whose roentgenograms were reviewed was free of abnormalities. However, the mean number of abnormal vertebral levels per patient did not differ by treatment group (isotretinoin group, 9.6 levels per patient; placebo group, 9.0 levels per patient; $P>.12$). In addition, there were no significant treatment group differences in the percentage of patients reporting neck or back arthralgias and/or stiffness at baseline (isotretinoin group, 50%; placebo group, 45%; $P>.56$).

Data on hyperostotic skeletal changes observed by roentgenography between baseline and 36 months are presented in Table 2. These changes consisted of progression of preexisting ossification of the anterior spinal ligament (Fig 1) and/or increases in bony excrescences along the anterior-superior or anterior-inferior margins of vertebral bodies (Fig 2). In comparison with the placebo group, more than twice the percent of patients in the isotretinoin group exhibited progression of cervical and/or thoracic hyperostotic vertebral abnormalities (40% vs 18%; $P<.001$). Although few patients demonstrated new skeletal involvement of previously unaffected vertebral levels, the percent of patients with new hyperostotic vertebral involvement was also significantly higher in the isotretinoin group (8% vs 1%; $P=.015$).

The potential risk factors shown in Table 1 did not significantly affect the risk of hyperostotic progression associated with isotretinoin treatment (data not shown). Among these risk factors, only male sex was independently associated with increased risk for hyperostotic progression (odds ratio, 2.09; 95% confidence interval, 1.01 to 4.32).

COMMENT

Our findings indicate that chronic, very-low-dose isotretinoin can induce hyperostotic skeletal changes in the cervical and thoracic spine similar to those reported in patients taking higher doses.[13-21] Roentgenographically, the changes we observed were similar to the axial skeletal changes of naturally occurring diffuse idiopathic skeletal hyperostosis[5] and appeared to be a continuation of a preexisting process rather than a unique or distinct pathologic change. As similarly reported by Pennes et al,[19] the hyperostoses in our pa-

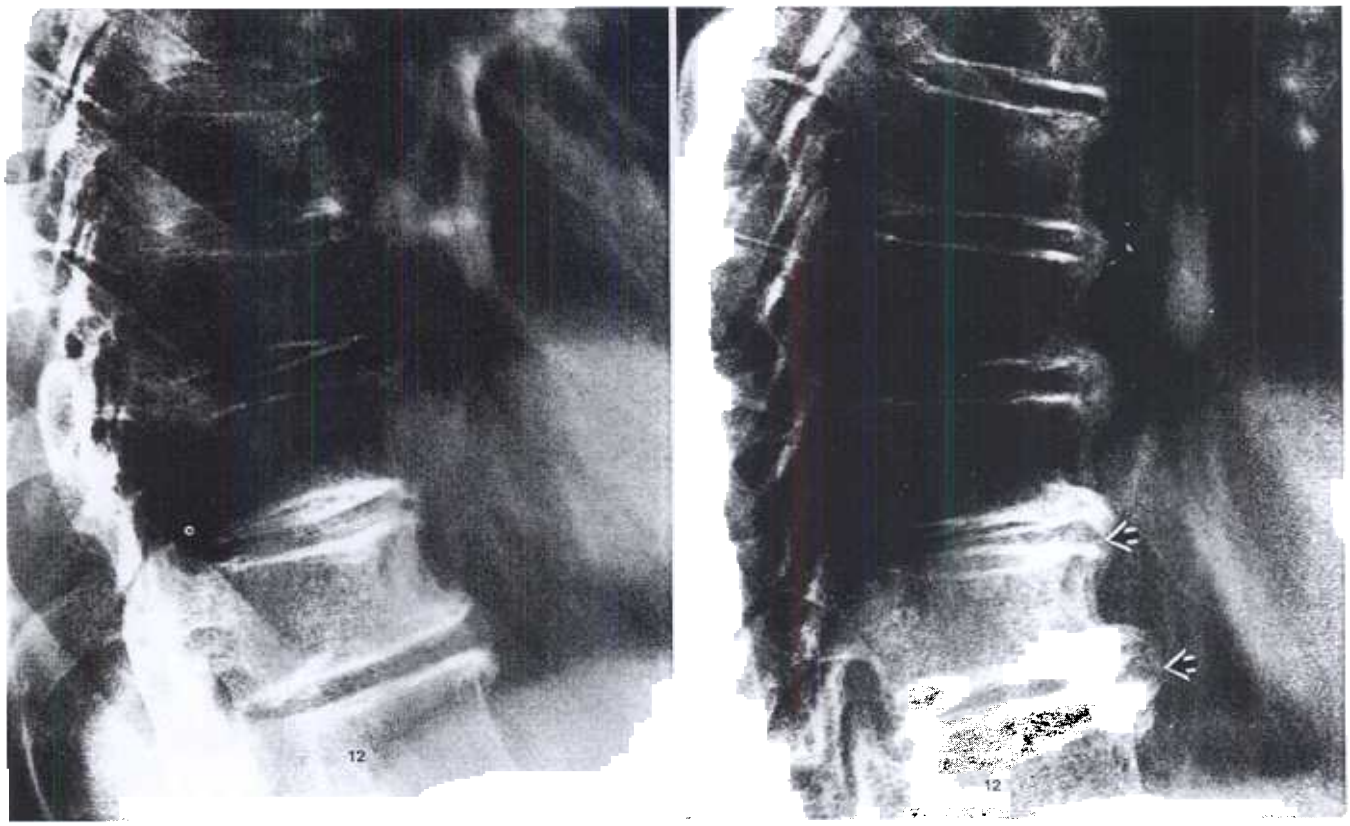

Fig 2.—Left, Baseline roentgenogram of a 74-year-old man showing mild hyperostosis at T8-T12. Right, Roentgenogram taken after 36 months of treatment with isotretinoin shows marked thickening of the anterior spinal ligament and extensive progression of horizontally oriented spurs at T10-11 and T11-12 (arrows).

tients were multifocal rather than diffuse with some vertebral levels affected while other areas of the spine remained completely free of hyperostotic change. The hyperostoses that progressed appeared, in many cases, initially as calcification and later as mature, ossified bone, as reported by others.[17-21] Because we limited our roentgenograms to lateral views of the cervical and thoracic spine, we are unable to report on potential extraspinal manifestations of chronic, very-low-dose isotretinoin. Although others have observed retinoid-induced calcification of the posterior longitudinal ligament,[15,16,19,33] we saw no hyperostotic change in the posterior cervical and thoracic spines of these patients.

While we did observe roentgenographic differences by treatment group, there were no significant treatment group differences in self-reports of back pain or stiffness over the 36 months of intervention in this random sample of patients. In addition, no patients in either the treatment or control group dropped out of the study due to arthralgias, back pain, or stiffness. Since we did not perform systematic measures of flexibility or range-of-motion studies in these patients, we cannot rule out subtle clinical effects. However, the location and magnitude of these roentgenographic changes make them unlikely to be of clinical importance.[4,33,34]

Further roentgenographic monitoring will be performed in the future to determine if the progression of hyperostotic skeletal changes seen in the isotretinoin group during the 36-month treatment phase of this study persists, worsens, or regresses after very-low-dose isotretinoin intervention ends.

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